

## REMARKS

With this Amendment, Applicants have amended Claims 26 and 27. After entry of the instant amendment, Claims 1, 3-18, 20-27, 29, 34-35, 37, 42, 44, 54-56. Attached herewith is Exhibit A (Version with Markings to Show Changes Made) and Exhibit B (Pending Claims After Entry of the Instant Amendment).

### **I. THE AMENDMENT OF THE CLAIMS**

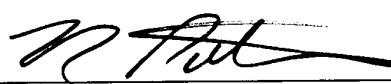
Claims 26 and 27 have been amended to correct dependency and a typographical error. Support for amended Claims 26 and 27 may be found, for example, in Claims 26 and 27 as originally filed and in the specification, for example, at page 44, lines 15 to 29.

## CONCLUSION

No fees in addition to the fees for additional claims indicated on the fee sheet filed herewith are believed due. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP, U.S. Deposit Account No. 16-1150 (Order No. 9196-022-999). A copy of this sheet is enclosed for accounting purposes.

Respectfully submitted,

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**EXHIBIT A**

**Claim Amendment: Version with Markings to Show Changes Made**

26. (Twice amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or [21] 22 in which each HH is independently [a] an altered D-enantiomeric peptide or peptide analogue [according to Claim 3].
27. (Twice amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a deleted D-enantiomeric peptide or peptide analogue [according to Claim 10].

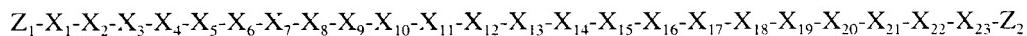


## EXHIBIT B

### Claim Amendment: Pending Claims After Entry of the Instant Amendment

1. An ApoA-I agonist compound comprising:

(i) a 22 to 29-residue D-enantiomeric peptide or peptide analogue which forms an amphipathic  $\alpha$ -helix in the presence of lipids and which comprises formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

$X_1$  is D-Ala (a), Gly (G), D-Gln (q), D-Asn (n), D-Asp (d) or D-Pro (p);

$X_2$  is a D-enantiomeric aliphatic residue;

$X_3$  is D-Leu (l) or D-Phe (f);

$X_4$  is a D-enantiomeric acidic residue;

$X_5$  is D-Leu (l) or D-Phe (f);

$X_6$  is D-Leu (l) or D-Phe (f);

$X_7$  is a D-enantiomeric hydrophilic residue;

$X_8$  is a D-enantiomeric acidic or a basic residue;

$X_9$  is D-Leu (l) or Gly (G);

$X_{10}$  is D-Leu (l), D-Trp (w) or Gly (G);

$X_{11}$  is a D-enantiomeric hydrophilic residue;

$X_{12}$  is a D-enantiomeric hydrophilic residue;

$X_{13}$  is Gly (G) or a D-enantiomeric aliphatic residue;

$X_{14}$  is D-Leu (l), D-Trp (w), Gly (G) or D-Nal;

$X_{15}$  is a D-enantiomeric hydrophilic residue;

$X_{16}$  is a D-enantiomeric hydrophobic residue;

$X_{17}$  is a D-enantiomeric hydrophobic residue;

$X_{18}$  is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;

$X_{19}$  is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;

$X_{20}$  is a D-enantiomeric basic residue;

$X_{21}$  is a D-enantiomeric aliphatic residue;

$X_{22}$  is a D-enantiomeric basic residue;

$X_{23}$  is absent or a D-enantiomeric basic residue;  
 $Z_1$  is  $R_2N-$  or  $RC(O)NR-$ ;  
 $Z_2$  is  $-C(O)NRR$ ,  $-C(O)OR$  or  $-C(O)OH$  or a salt thereof;  
each R is independently -H, ( $C_1-C_6$ ) alkyl, ( $C_1-C_6$ ) alkenyl, ( $C_1-C_6$ ) alkynyl,  
( $C_5-C_{20}$ ) aryl, ( $C_6-C_{26}$ ) alkaryl, 5-20 membered heteroaryl, 6-26 membered alkheteroaryl or a  
1 to 7-residue peptide or peptide analogue in which one or more bonds between residues  
1 through 7 are independently a substituted amide, an isostere of an amide or an amide  
mimetic; and

each " - " between residues  $X_1$  through  $X_{23}$  independently designates an amide  
linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 14 to 28-residue deleted D-enantiomeric peptide or peptide analogue according  
to formula (I) in which at least one and up to eight of residues  $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8,$   
 $X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, X_{21}$  and  $X_{22}$  are optionally deleted; or

(iii) a 22 to 29-residue altered D-enantiomeric peptide or peptide analogue according  
to formula (I) in which at least one of residues  $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11},$   
 $X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, X_{21}, X_{22}$  or  $X_{23}$  is conservatively substituted with  
another D-enantiomeric residue.

3. The ApoA-I agonist compound of Claim 1 which is the altered D-enantiomeric  
peptide or peptide analogue according to formula (I).

4. The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophobic  
residues are fixed according to formula (I) and at least one non-fixed residue is conservatively  
substituted with another D-enantiomeric residue.

5. The ApoA-I agonist compound of Claim 4 in which:

$X_1$  is D-Pro (p), Gly (G) or D-Ala (a);  
 $X_2$  is D-Ala (a), D-Leu (l) or D-Val (v);  
 $X_3$  is D-Leu (l) or D-Phe (f);

$X_5$  is D-Leu (l) or D-Phe (f);

$X_6$  is D-Leu (l) or D-Phe (f);

$X_9$  is D-Leu (l) or Gly (G);

$X_{10}$  is D-Leu (l), D-Trp (w) or Gly (G);

$X_{13}$  is D-Leu (l), Gly (G) or D-Aib;

$X_{14}$  is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);

$X_{16}$  is D-Ala (a), D-Nal, D-Trp (w), Gly (G), D-Leu (l) or D-Phe (f);

$X_{17}$  is D-Leu (l), Gly (G) or D-Nal;

$X_{21}$  is D-Leu (l); and

at least one of  $X_4$ ,  $X_7$ ,  $X_8$ ,  $X_{11}$ ,  $X_{12}$ ,  $X_{15}$ ,  $X_{18}$ ,  $X_{19}$ ,  $X_{20}$ ,  $X_{22}$  and  $X_{23}$  is conservatively substituted with another D-enantiomeric residue.

6. The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophilic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

7. The ApoA-I agonist compound of Claim 6 in which:

$X_4$  is D-Asp (d) or D-Glu (e);

$X_7$  is D-Lys (k), D-Arg (r) or D-Orn;

$X_8$  is D-Asp (d) or D-Glu (e);

$X_{11}$  is D-Asn (n) or D-Gln (q);

$X_{12}$  is D-Glu (e) or D-Asp (d);

$X_{15}$  is D-Asp (d) or D-Glu (e);

$X_{18}$  is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

$X_{19}$  is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

$X_{20}$  is D-Lys (k) or D-Orn;

$X_{22}$  is D-Lys (k) or D-Orn;

$X_{23}$  is absent or D-Lys (k); and

at least one of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_5$ ,  $X_6$ ,  $X_9$ ,  $X_{10}$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{16}$ ,  $X_{17}$  and  $X_{21}$  is conservatively substituted with another D-enantiomeric residue.

8. The ApoA-I agonist compound of Claim 7 in which  $X_3$  is D-Leu (l) or D-Phe (f),  $X_6$  is D-Phe (f),  $X_9$  is D-Leu (l) or Gly (G),  $X_{10}$  is D-Leu (l) or D-Trp (w) or Gly (G) and at least one of  $X_1$ ,  $X_2$ ,  $X_5$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{16}$ ,  $X_{17}$  and  $X_{21}$  is conservatively substituted with another D-enantiomeric residue.
9. The ApoA-I agonist compound of Claim 4 or 6 in which the substituting D-enantiomeric residue is classified within the same sub-category as the substituted D-enantiomeric residue.
10. The ApoA-I agonist compound of Claim 1 which is the deleted D-enantiomeric peptide or peptide analogue according to formula (I).
11. The ApoA-I agonist compound of Claim 10 in which one or two helical turns of the peptide or peptide analogue is optionally deleted.
12. The ApoA-I agonist compound of Claim 1 which is a 22-23 residue D-enantiomeric peptide or peptide analogue according to formula (I).
13. The ApoA-I agonist compound of Claim 12 in which:  
the "-" between residues designates -C(O)NH-;  
 $Z_1$  is  $H_2N-$ ; and  
 $Z_2$  is -C(O)OH or a salt thereof.
14. The ApoA-I agonist compound of Claim 13, in which:  
 $X_1$  is D-Ala (a), Gly (G), D-Asn (n), D-Gln (q), D-Asp (d) or D-Pro (p);  
 $X_2$  is D-Ala (a), D-Val (v) or D-Leu (l);  
 $X_3$  is D-Leu (l) or D-Phe (f);  
 $X_4$  is D-Asp (d) or D-Glu (e);  
 $X_5$  is D-Leu (l) or D-Phe (f);  
 $X_6$  is D-Leu (l) or D-Phe (f);  
 $X_7$  is D-Lys (k), D-Arg (r) or D-Orn;

$X_8$  is D-Asp (d) or D-Glu (e);  
 $X_9$  is D-Leu (l) or Gly (G);  
 $X_{10}$  is D-Leu (l), D-Trp (w) or Gly (G);  
 $X_{11}$  is D-Asn (n) or D-Gln (q);  
 $X_{12}$  is D-Glu (e) or E-Asp (d);  
 $X_{13}$  is Gly (G), D-Leu (l) or D-Aib;  
 $X_{14}$  is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);  
 $X_{15}$  is D-Asp (d) or D-Glu (e);  
 $X_{16}$  is D-Ala (a), D-Nal, D-Trp (w), D-Leu (l), D-Phe (f) or Gly (G);  
 $X_{17}$  is Gly (G), D-Leu (l) or D-Nal;  
 $X_{18}$  is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;  
 $X_{19}$  is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;  
 $X_{20}$  is D-Lys (k) or D-Orn;  
 $X_{21}$  is D-Leu (l);  
 $X_{22}$  is D-Lys (k) or D-Orn; and  
 $X_{23}$  is absent or D-Lys (k).

15. The ApoA-I agonist compound of Claim 14, in which  $X_{23}$  is absent.
16. The ApoA-I agonist compound of Claim 13 or 14, in which one of  $X_{18}$  or  $X_{19}$  is D-Gln (q) or D-Asn (n) and the other of  $X_{18}$  or  $X_{19}$  is D-Lys (k) or D-Orn.
17. The ApoA-I agonist compound of Claim 14 in which each of  $X_9$ ,  $X_{10}$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{15}$  and  $X_{17}$  is other than Gly (G).
18. The ApoA-I agonist compound of Claim 14 in which one of  $X_9$ ,  $X_{10}$ ,  $X_{13}$ ,  $X_{14}$ ,  $X_{15}$  and  $X_{17}$  is Gly (G) and the others are other than Gly (G).
20. A multimeric ApoA-I agonist compound which comprises formula (II):

(II)



or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

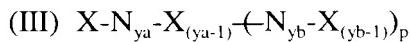
each "HH" is independently a peptide or peptide analogue according to

Claim 1;

each "LL" is independently a bifunctional linker; and

each " - " independently designates a covalent linkage.

21. A multimeric ApoA-I agonist compound which comprises formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently  $HH-\text{---}LL_m-\text{---}HH-\text{---}nLL_m-\text{---}HH$ ;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

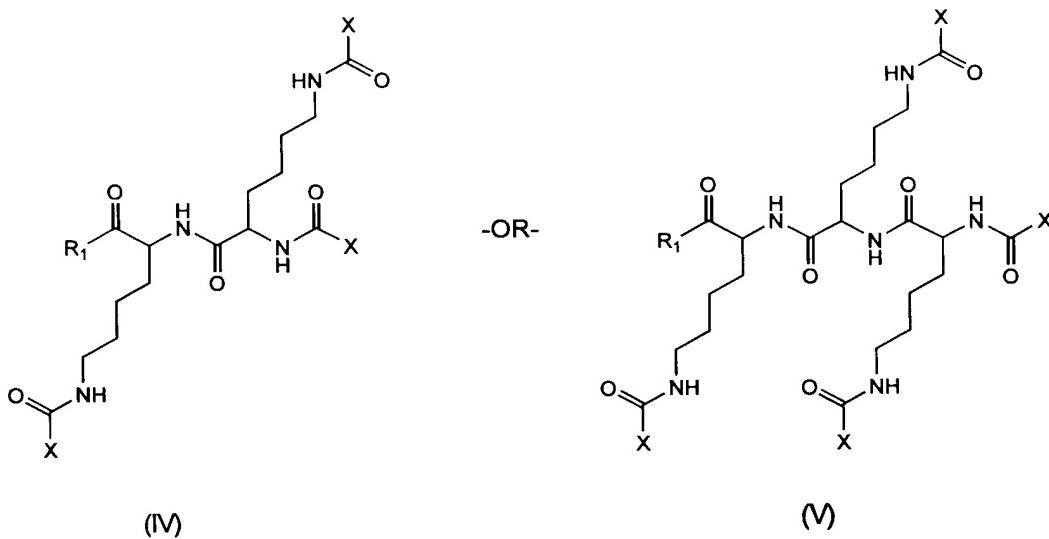
$N_{y_a}$  and  $N_{y_b}$  are each independently a multifunctional linking moiety where  $y_a$  and  $y_b$  represent the number of functional groups on  $N_{y_a}$  and  $N_{y_b}$ , respectively;

each  $y_a$  or  $y_b$  is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

each "—" independently designates a covalent bond.

22. A multimeric ApoA-I agonist compound which comprises formula (IV) or (V):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently HH-(LL<sub>m</sub>-HH)<sub>n</sub>LL<sub>m</sub>-HH;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R<sub>1</sub> is -OR or -NRR; and

each R is independently -H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkenyl, (C<sub>1</sub>-C<sub>6</sub>) alkynyl;

(C<sub>5</sub>-C<sub>20</sub>) aryl (C<sub>6</sub>-C<sub>26</sub>) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl.

23. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which the bifunctional linker is cleavable.

24. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which n is 0.

25. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which m is 0.
26. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently an altered D-enantiomeric peptide or peptide analogue.
27. The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a deleted D-enantiomeric peptide or peptide analogue.
29. An ApoA-I agonist-lipid complex comprising an ApoA-I agonist compound and a lipid, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.
34. The ApoA-I agonist-lipid complex of Claim 29 in which the lipid is sphingomyelin.
35. The ApoA-I agonist-lipid complex of Claim 34 which is in the form of a lyophilized powder.
37. A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.
42. The pharmaceutical composition of Claim 37, in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist compound and a lipid.

44. A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

54. A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

55. The method of Claim 44 or 54 in which said subject is a human.

56. The method of Claim 44 or 54 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist is administered to said subject.